Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 287-622 are pending in the application, with 287, 300, 319, 340, 351, 362, 374, 389, 404, 416, 431, 446, 459, 476, 492, 507, 518, 535, 553, 565, 580, 595, and 608 being the independent claims. The Examiner has indicated that claim 300-317, 340-350, 374, 375, 377-380, 382-387, 416, 417, 419-429, 459-474, and 595-606 are allowed. Claims 299, 318, 339, 362, 373, 376, 381, 388, 391, 403, 404, 405, 415, 418, 430, 433, 445, 458, 475, 491, 494, 506, 517, 522, 534, 540, 552, 564, 579, 594, 607, 609, 610, 615, and 622 have been amended. The amendments have been made to correct clear typographical or clerical errors, to more particularly point out and distinctly claim the subject matter Applicants regard as the invention, and/or to make explicit that which was previously implicit in the claims. *See Interactive Pictures Corp. v. Infinite Pictures Inc.*, 61 U.S.P.Q.2d 1152, 1157 (Fed. Cir. 2001). Support for the amendments may be found throughout the specification. It is not believed that any of these amendments narrow the claims. These amendments are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Claim Interpretation

The Examiner has interpreted "mature DR5 polypeptide" to mean the "one disclosed in the specification as the mature form of ATCC 97920 expression product or SEQ ID NO:2 from amino acids +1 to +360 . . . ." Paper No. 27 at page 2. The Examiner has similarly interpreted "DR5 polypeptide" to mean "the disclosed DR5 sequence in the specification that is the expression product of the cDNA of ATCC 97920 or SEQ ID NO:2 from amino acids -51 to +360 . . . ." *Id.* Applicants do not disagree with these interpretations.

Claim Objections

The Examiner has objected to claims 381, 607, and 615 due to improper dependencies. Paper No. 27 at page 2. Applications thank the Examiner for pointing out these typographical errors. The claims have been amended to reflect proper dependencies, and thus properly limit the subject matter of the claims from which they depend. Accordingly, Applicants respectfully request that these objections be withdrawn.

Rejections under 35 U.S.C. § 112, Second Paragraph

(a) The Examiner has rejected claims 381, 607, and 615 under 35 U.S.C. § 112, second paragraph, for lacking sufficient antecedent basis for certain recitations in the claims. As discussed *supra*, these claims contained typographical errors. These errors have been corrected, thereby rendering these rejections moot. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw these

rejections. Upon further review, Applicants also noted a clerical error in claim 405, which has been corrected by providing proper reference to the antecedent polypeptide fragment of claim 404.

(b) The Examiner has rejected claims 299, 318, 339, 373, 388, 403, 415, 430, 445, 458, 475, 491, 506, 517, 534, 552, 564, 579, 594, 607, and 622 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite as to which polypeptide is supposed to be produced by the claimed method. Paper No. 27 at page 3. Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have amended claims 299, 318, 339, 373, 388, 403, 415, 430, 445, 458, 475, 491, 506, 517, 534, 552, 564, 579, 594, 607, and 622 to specifically recite the polypeptide, polypeptide fragment, or protein the respective claimed methods are intended to produce, subject matter that was previously implicit in the claims. Based on these remarks, Applicants respectfully request that this rejection be reconsidered, and further that it be withdrawn.

(c) The Examiner has rejected claims 362, 376, 391, 404, 418, 433, 494, 522, 540, and 610 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite as to the spatial relationship of the claimed polypeptide fragments relative to a mature DR5 polypeptide. The Examiner maintains that it is unclear whether such a polypeptide fragment "is solely responsible for inducing apoptosis, or whether it must rely on some part of the mature DR5 polypeptide to induce apoptosis." Paper No. 27 at page 4.

Similarly, the Examiner has rejected claim 609 because it is allegedly unclear as to how the claimed polypeptide fragment functions with respect to binding TRAIL. Paper No. 27 at page 4.

Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have amended claims 362, 376, 391, 404, 418, 433, 494, 522, 540, 609, and 610 to indicate that DR5 variants or DR5 polypeptides, in which the claimed polypeptide fragments have been substituted for analogous portions, have the required function, *i.e.*, either inducing apoptosis *in vitro* when overexpressed in human breast carcinoma cells (*see*, *e.g.*, the specification at page 53, lines 5-8 and Fig. 5A), or binding TRAIL.

Based on these remarks, Applicants respectfully request that this rejection be reconsidered, and further that it be withdrawn.

Rejections under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 404-415, 418, 433, 494, 522, 540, 609, and 610 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Specifically, the Examiner alleges that the specification does not provide enablement for a

> (1) . . .polynucleotide comprising a nucleic acid which encodes a polypeptide (a) consisting of an amino acid sequence less than 90% identical to amino acids 1-133 of SEQ ID NO:2 . . . wherein said polypeptide must bind TRAIL or (b) consisting of an amino acid sequence less than 90% identical to amino acids 158-360 of SEQ ID NO:2 . . . wherein said polypeptide induces [apoptosis]; or (2) [a] polynucleotide comprising a nucleic acid which encodes a polypeptide fragment at least 90% identical to amino acids 273-340 of SEQ ID NO:2 or a 5-50 contiguous amino acid-long fragment of SEQ ID NO:2 . . . which induces apoptosis.

Paper No. 27 at page 5.

Solely to advance prosecution, and not in acquiescence to the Examiner's rejection, Applicants have amended claims 405, 418, 433, 494, 522, 540, 609, and 610 to indicate that DR5 variants or DR5 polypeptides, in which the claimed polypeptide fragments have been substituted for analogous portions, have the required function, *i.e.*, either inducing apoptosis *in vitro* when overexpressed in human breast carcinoma cells, or binding TRAIL.

Based on these remarks, Applicants respectfully request that this rejection be reconsidered, and further that it be withdrawn.

Rejections under 35 U.S.C. § 102

The Examiner has rejected claims 492-495, 507-508, 518-523, 555-541, and 608-611 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,072,047 (the '047 patent). In making this rejection, the Examiner specifically cites U.S. Patent Appl. No. 08/815,255, filed on March 12, 1997 (the "March 12, 1997 priority document"), relied upon under 35 U.S.C. § 120 in the '047 patent, for disclosure of a DNA fragment encoding a polypeptide fragment which, according to the Examiner, is identical to amino acids 256-306 of SEQ ID NO:2 of the present application. *See* Paper No. 27 at page 7.

Applicants respectfully traverse. Applicants assert that they were in possession of sequences relevant to the subject matter of claims 492-495, 507-508, 518-523, 555-541, and 608-611, in the United States, before March 12, 1997. In support of this assertion, Applicants submit herewith a Declaration under 37 C.F.R. § 1.131 by inventors Jian Ni, Reiner L. Gentz, Guo-Liang Yu, and Craig A. Rosen, with attached

Exhibit A, attesting to this fact. The attached Declaration has been executed by Inventors Gentz and Rosen. Inventors Ni and Yu were not immediately available to sign the Declaration. However, Applicants' representative expects to receive signed copies of the Declaration from these inventors in the near future, and will forward the complete Declaration as soon as possible. Since Applicants were in possession of the relevant sequences prior to March 12, 1997, the disclosure of the March 12, 1997 priority document is unavailable as a reference.

Based on these remarks and the attached Declaration, Applicants respectfully request that the rejection under 35 U.S.C. § 102(e) over the '047 patent be reconsidered, and further that it be withdrawn.

Rejections under 35 U.S.C. § 103

(a) The Examiner has rejected claims 492-552 and 608-622 under 35 U.S.C. § 103(a)/102(e) as allegedly being rendered obvious by the '047 patent. In making this rejection, the Examiner specifically cites the March 12, 1997 priority document, relied upon under 35 U.S.C. § 120 in the '047 patent, for disclosure of a DNA fragment encoding a polypeptide fragment which, according to the Examiner, is identical to amino acids 256-306 of SEQ ID NO:2 of the present application. The Examiner alleges that the '047 patent later shows that the fragment disclosed in the March 12, 1997 priority document inherently functions within a mature DR5 to induce apoptosis. *See* Paper No. 27 at pages 8 and 9.

Applicants respectfully traverse. Applicants assert that they were in possession of sequences relevant to the subject matter of claims 492-552 and 608-622, in the United

States, before March 12, 1997. In support of this assertion, Applicants submit herewith a Declaration under 37 C.F.R. § 1.131 by inventors Jian Ni, Reiner L. Gentz, Guo-Liang Yu, and Craig A. Rosen attesting to this fact. Accordingly, the disclosure of the March 12, 1997 priority document is unavailable as a reference.

(b) The Examiner has rejected claims 287-299, 319, 326-339, 351, 353-373, 389, 391-415, 431, 433-458, 476, 478-491, 553-565, and 567-594 under 35 U.S.C. § 103(a)/102(e) as allegedly being rendered obvious by the '047 patent. In making this rejection, the Examiner cites U.S. Patent Appl. No. 08/799,861, filed on February 13, 1997 (the "February 13, 1997 priority document"), relied upon under 35 U.S.C. § 120 in the '047 patent, for disclosure of an isolated mature TRAIL-R protein, in addition to the March 12, 1997 priority document described above. The Examiner alleges that, based on the disclosures of the February 13, 1997 and March 12, 1997 priority documents, the above listed claims would be rendered obvious. *See* Paper No. 27 at pages 9-11.

Applicants respectfully traverse. Applicants assert that they were in possession of sequences relevant to the subject matter of claims 287-299, 319, 326-339, 351, 353-373, 389, 391-415, 431, 433-458, 476, 478-491, 553-565, and 567-594, in the United States, before March 12, 1997. In support of this assertion, Applicants submit herewith a Declaration under 37 C.F.R. § 1.131 by inventors Jian Ni, Reiner L. Gentz, Guo-Liang Yu, and Craig A. Rosen, with attached Exhibit A, attesting to this fact (*see supra*). Accordingly, the disclosure of the March 12, 1997 priority document is unavailable as a reference.

Furthermore, the February 13, 1997 priority document relied upon by the Examiner is insufficient to sustain any such *prima facie* case on its own.

To establish a *prima facie* case of obviousness under 35 U.S.C. § 103, the Examiner must show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device, and that the invention could be obtained *with a reasonable expectation of success*. *See In re Vaeck*, 20 U.S.P.Q.2d 1438, 1443 (Fed. Cir. 1991)(emphasis added). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art cited. *Id.*

The Examiner argues that "one of ordinary skill in the art could have readily envisioned all the degenerate sequences that encoded the TRAIL-R protein . . . . This knowledge was the basis of making the degenerate oligo primers of U.S. Patent 6,072,047 that allowed TRAIL-R DNA to be obtained." Paper No. 27 at page 10. Especially as applied to the February 13, 1997 priority document standing alone, Applicants respectfully disagree.

The February 13, 1997 priority document discloses isolation of a mature protein which apparently binds TRAIL, and three short peptide sequences. *See* U.S. Patent Application No. 08/799,861 at page 18, lines 9-31. Of these three peptide sequences, one (VCEC, deleted from the '047 patent) does not correspond at all to the TRAIL-R sequence later disclosed in the '047 patent, and one (SGEVELSSV) aligns only partially to the TRAIL-R sequence later disclosed in the '047 patent. Thus, only one of three peptide sequences disclosed in the February 13, 1997 priority document corresponds exactly to the TRAIL-R amino acid sequence later disclosed in the '047 patent. As pointed out by the Examiner, the February 13, 1997 priority document does contemplate nucleic acids encoding the disclosed peptides, and suggests making degenerate

oligonucleotide primers. *See* U.S. Patent Application No. 08/799,861 at page 15, lines 9-24.

Even assuming that "one of ordinary skill in the art could have readily envisioned all the degenerate sequences that encoded the TRAIL-R protein" as argued by the Examiner, the skilled artisan would have had no reasonable expectation of success in this case, since two out of three of the disclosed peptides were incorrect. Indeed, even the inventors of the '047 patent were unsuccessful, since they ultimately had to rely on new matter to obtain a polynucleotide fragment. The March 12, 1997 priority document discloses that

> [t]he amino acid sequence of *additional* tryptic digest peptide fragments of TRAIL-R was determined. Degenerate oligonucleotides, based upon the amino acid sequence of two of the peptides, were prepared. A TRAIL-R DNA fragment was isolated and amplified by polymerase chain reaction (PCR) using the degenerate oligonucleotides.

U.S. Patent Application No. 08/815,255, page 19, lines 14-17 (emphasis added).

Further details of the inventors' lack of success based on the disclosure of the February 13, 1997 priority document, and of the considerable additional experimentation that was required, can be found in Walczak *et al.*, (*EMBO J. 16*:5386-5397 (September 1, 1997)), attached hereto as Exhibit B. In Exhibit B, '047 patent inventors Rauch, Walczak, and colleagues disclose the specific peptide sequences which were ultimately used to isolate the nucleic acid sequence shown in Figure 1 of the March 12, 1997 priority document. These peptides, LLVPANEGDPTETLR (peptide T6), and DTLYTMLIK (peptide T8), were identified in a *second* protein purification. *See* Walczak *et al.*, page 5388, column 1. Neither of these specific peptides are disclosed in

the February 13, 1997 priority document, nor in any of the later priority documents. Furthermore, the authors describe that PCR reactions were carried out using any of 8 different degenerate PCR primers synthesized according to peptide T6 combined with any of 24 different degenerate PCR primers synthesized according to peptide T8. Of these 192 possible primer combinations, the authors disclose only one primer pair that resulted in the correct PCR product.[1] *See* Walczak *et al.*, page 5394, column 2.

Since even the inventors were forced to identify additional peptide sequences, and to test myriad degenerate oligonucleotides based on these new peptide sequences in order to obtain the polynucleotide fragment disclosed in the March 12, 1997 priority document, it is clear that one of ordinary skill in the art, as of the filing date of the February 13, 1997 priority document had no reasonable expectation of success that the present invention could be obtained without the hindsight provided by the later filings.

Based on these remarks and the attached Declaration, Applicants respectfully request that all rejections under 35 U.S.C. § 103(a), as applied to the pending claims, be withdrawn.

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[1] Applicants note that a portion of peptide T6, VPANEGD, was disclosed in the February 13, 1987 priority document. However the degenerate oligonucleotide based on peptide T6 which was ultimately successful in amplifying the DNA fragment shown in Figure 1 of the March 12, 1997 priority document, AAY GAR GGN GAY CCN ACT GAR AC (*see* Walczak *et al.*, page 5390, Figure 3A, and page 5394, column 2), encodes the peptide NEGDPTET, which only partially overlaps with the peptide disclosed in the February 13, 1987 priority document.

Change of Correspondence Address

Paper No. 27 was once again sent to Applicants directly, using the original attorney docket number. On August 12, 1999, the PTO was notified that prosecution of this application had been transferred to the law firm of Sterne, Kessler, Goldstein & Fox, P.L.L.C. at the address shown below. Furthermore, the docket number was changed. Applicants have now submitted copies of the Change of Correspondence Address form and the post card stamped as received by the PTO on August 12, 1999 several times. Applicants once again respectfully request that the records relating to this application be updated, and that all future correspondence be sent to Sterne, Kessler, Goldstein & Fox, P.L.L.C., Customer Number 28730, using the attorney docket number 1488.1310002/EKS/EJH, as shown at the top of this pleading.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

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Date: June 4, 2002

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Version with markings to show changes made

Please amend claims 299, 318, 339, 362, 373, 376, 381, 388, 391, 403, 404, 405, 415, 418, 430, 433, 445, 458, 475, 491, 494, 506, 517, 522, 534, 540, 552, 564, 579, 594, 607, 609, 610, 615, and 622 as follows:

299. (Once Amended) A method of producing [a] the polypeptide encoded by the polynucleotide of claim 287, comprising culturing [the] a host cell [of claim 297] comprising said polynucleotide under conditions such that said polypeptide is expressed, and recovering said polypeptide.

318. (Once Amended) A method of producing [a] the polypeptide encoded by the polynucleotide of claim 305, comprising culturing [the] a host cell [of claim 316] comprising said polynucleotide under conditions such that said polypeptide is expressed, and recovering said polypeptide.

339. (Once Amended) A method of producing [a] the polypeptide encoded by the polynucleotide of claim 326, comprising culturing [the] a host cell [of claim 337] comprising said polynucleotide under conditions such that said polypeptide is expressed, and recovering said polypeptide.

362. (Once Amended) An isolated polynucleotide comprising a nucleic acid which encodes a polypeptide fragment at least 90% identical to amino acids 158 to 360 of SEQ ID NO:2; and

wherein a DR5 variant polypeptide consisting of amino acids 1 to 360 of SEQ ID NO:2, with the exception that amino acids 158-360 of SEQ ID NO:2 are deleted and replaced with said polypeptide fragment, induces apoptosis *in vitro* when over-expressed in human breast carcinoma cells [said polypeptide fragment is capable of functioning as a functional domain within a mature DR5 polypeptide to induce apoptosis].

373. (Once Amended) A method of producing [a] the polypeptide fragment encoded by the polynucleotide of claim 362, comprising culturing [the] a host cell [of claim 371] comprising said polynucleotide under conditions such that said polypeptide fragment is expressed, and recovering said polypeptide fragment.

376. (Once Amended) The polynucleotide of claim 374, wherein said first nucleic acid encodes a polypeptide fragment; and wherein a DR5 variant polypeptide consisting of amino acids 1 to 360 of SEQ ID NO:2, with the exception that amino acids 158-360 of SEQ ID NO:2 are deleted and replaced with said polypeptide fragment,

induces apoptosis *in vitro* when over-expressed in human breast carcinoma cells [which is capable of functioning as a functional domain within a mature DR5 polypeptide to induce apoptosis].

381. (Once Amended) A method of producing a vector that comprises inserting the polynucleotide of claim [96] 374 into a vector.

388. (Once Amended) A method of producing [a] the polypeptide fragment encoded by the polynucleotide of claim 376, comprising culturing [the] a host cell [of claim 386] comprising said polynucleotide under conditions such that said polypeptide fragment is expressed, and recovering said polypeptide fragment.

391. (Once Amended) The polynucleotide of claim 389, which encodes a polypeptide fragment, wherein a DR5 polypeptide consisting of amino acids 1 to 360 of SEQ ID NO:2, with the exception that amino acids 158-360 of SEQ ID NO:2 are deleted and replaced with said polypeptide fragment, induces apoptosis *in vitro* when over-expressed in human breast carcinoma cells [which is capable of functioning as a functional domain within a mature DR5 polypeptide to induce apoptosis].

403. (Once Amended) A method of producing [a] the polypeptide fragment encoded by the polynucleotide of claim 391, comprising culturing [the] a host cell [of claim 401] comprising said polynucleotide under conditions such that said polypeptide fragment is expressed, and recovering said polypeptide fragment.

404. (Once Amended) An isolated polynucleotide comprising a nucleic acid which encodes a polypeptide fragment at least 90% identical to amino acids 273 to 340 of SEQ ID NO:2;

wherein a DR5 variant polypeptide consisting of amino acids 1 to 360 of SEQ ID NO:2, with the exception that amino acids 273-340 of SEQ ID NO:2 are deleted and replaced with said polypeptide fragment, induces apoptosis *in vitro* when over-expressed in human breast carcinoma cells [said polypeptide fragment is capable of functioning as a functional domain within a mature DR5 polypeptide to induce apoptosis].

405. (Once Amended) The polynucleotide of claim 404, wherein said polypeptide fragment is at least 95% identical to amino acids 273 to 340 of SEQ ID NO:2.

415. (Once Amended) A method of producing [a] the polypeptide fragment encoded by the polynucleotide of claim 404, comprising culturing [the] a host cell [of claim 413] comprising said polynucleotide under conditions such that said polypeptide fragment is expressed, and recovering said polypeptide fragment.

418. (Once Amended) The polynucleotide of claim 416, wherein said first nucleic acid encodes a polypeptide fragment, and wherein a DR5 variant polypeptide consisting of amino acids 1 to 360 of SEQ ID NO:2, with the exception that amino acids 273-340 of SEQ ID NO:2 are deleted and replaced with said polypeptide fragment, induces apoptosis *in vitro* when over-expressed in human breast carcinoma cells [which is capable of functioning as a functional domain within a mature DR5 polypeptide to induce apoptosis].

430. (Once Amended) A method of producing [a] the polypeptide fragment encoded by the polynucleotide of claim 418, comprising culturing [the] a host cell [of claim 428] comprising said polynucleotide under conditions such that said polypeptide fragment is expressed, and recovering said polypeptide fragment.

433. (Once Amended) The polynucleotide of claim 431, wherein said nucleic acid encodes a polypeptide fragment, and wherein a DR5 polypeptide consisting of amino acids 1 to 360 of SEQ ID NO:2, with the exception that amino acids 273-340 of SEQ ID NO:2 are deleted and replaced with said polypeptide fragment, induces apoptosis *in vitro* when over-expressed in human breast carcinoma cells [which is capable of functioning as a functional domain within a mature DR5 polypeptide to induce apoptosis].

445. (Once Amended) A method of producing [a] the polypeptide fragment encoded by the polynucleotide of claim 433, comprising culturing [the] a host cell [of claim 443] comprising said polynucleotide under conditions such that said polypeptide fragment is expressed, and recovering said polypeptide fragment.

458. (Once Amended) A method of producing [a] the polypeptide encoded by the polynucleotide of claim 446 comprising culturing [the] a host cell [of claim 456] comprising said polynucleotide under conditions such that said polypeptide is expressed, and recovering said polypeptide.

475. (Once Amended) A method of producing [a] the polypeptide encoded by the polynucleotide of claim 462 comprising culturing [the] a host cell [of claim 473] comprising said polynucleotide under conditions such that said polypeptide is expressed, and recovering said polypeptide.

491. (Once Amended) A method of producing [a] the polypeptide encoded by the polynucleotide of claim 476 comprising culturing [the] a host cell [of claim 489]

comprising said polynucleotide under conditions such that said polypeptide is expressed, and recovering said polypeptide.

494. (Once Amended) The polynucleotide of claim 492, which encodes a polypeptide fragment, wherein a DR5 polypeptide consisting of amino acids 1 to 360 of SEQ ID NO:2, with the exception that the amino acids encoded by said 30 contiguous amino acids are deleted and replaced with said polypeptide fragment, induces apoptosis *in vitro* when over-expressed in human breast carcinoma cells [which is capable of functioning as a functional domain within a mature DR5 polypeptide to induce apoptosis].

506. (Once Amended) A method of producing [a] the polypeptide encoded by the polynucleotide of claim 492 comprising culturing [the] a host cell [of claim 502] comprising said polynucleotide under conditions such that said polypeptide is expressed, and recovering said polypeptide.

517. (Once Amended) A method of producing a polypeptide comprising the at least 50 contiguous amino acids encoded by the polynucleotide of claim 507 comprising culturing [the] a host cell [of claim 515] comprising said polynucleotide under conditions such that said polypeptide is expressed, and recovering said polypeptide.

522. (Once Amended) The polynucleotide of claim 518, which hybridizes to the complement of nucleotides 754 to 1362 of SEQ ID NO:1, and which encodes a polypeptide fragment, wherein a DR5 variant polypeptide consisting of amino acids 1 to 360 of SEQ ID NO:2, with the exception that amino acids 158-360 of SEQ ID NO:2 are deleted and replaced with said polypeptide fragment, induces apoptosis *in vitro* when over-expressed in human breast carcinoma cells [which is capable of functioning as a functional domain within a mature DR5 polypeptide to induce apoptosis].

534. (Once Amended) A method of producing [a] the polypeptide fragment encoded by the polynucleotide of claim 522 comprising culturing [the] a host cell [of claim 532] comprising said polynucleotide under conditions such that said polypeptide fragment is expressed, and recovering said polypeptide fragment.

540. (Once Amended) The polynucleotide of claim 535, wherein said first nucleic acid encodes a polypeptide fragment, and wherein a DR5 variant polypeptide consisting of amino acids 1 to 360 of SEQ ID NO:2, with the exception that amino acids 158 to 360 of SEQ ID NO:2 are deleted and replaced with said polypeptide fragment, induces apoptosis *in vitro* when over-expressed in human breast carcinoma cells [which

is capable of functioning as a functional domain within a mature DR5 polypeptide to induce apoptosis].

552. (Once Amended) A method of producing [a] the polypeptide fragment encoded by the polynucleotide of claim 540 comprising culturing [the] a host cell [of claim 540] comprising said polynucleotide under conditions such that said polypeptide fragment is expressed, and recovering said polypeptide fragment.

564. (Once Amended) A method of producing [a] the polypeptide encoded by the polynucleotide of claim 553 comprising culturing [the] a host cell [of claim 562] comprising said polynucleotide under conditions such that said polypeptide is expressed, and recovering said polypeptide.

579. (Once Amended) A method of producing a polypeptide comprising the amino acids encoded by the polynucleotide of claim 565, comprising culturing [the] a host cell [of claim 577] comprising said polynucleotide under conditions such that said polypeptide is expressed, and recovering said polypeptide.

594. (Once Amended) A method of producing [a] the [polypeptide] protein encoded by the polynucleotide of claim 580 comprising culturing [the] a host cell [of claim 592] comprising said polynucleotide under conditions such that said [polypeptide] protein is expressed, and recovering said [polypeptide] protein.

607. (Once Amended) A method of producing [a] the polypeptide encoded by the polynucleotide of claim 595 comprising culturing [the] a host cell [of claim 604] comprising said polynucleotide under conditions such that said polypeptide is expressed, and recovering said polypeptide.

609. (Once Amended) The polynucleotide of claim 608, wherein a DR5 variant polypeptide consisting of amino acids 1 to 360 of SEQ ID NO:2, with the exception that 50 contiguous amino acids of SEQ ID NO:2 are deleted and replaced with said polypeptide fragment, binds TRAIL [wherein said nucleic acid encodes a polypeptide fragment capable of functioning as a functional domain within a DR5 extracellular domain to bind TRAIL].

610. (Once Amended) The polynucleotide of claim 608, wherein a DR5 variant polypeptide consisting of amino acids 1 to 360 of SEQ ID NO:2, with the exception that 50 contiguous amino acids of SEQ ID NO:2 are deleted and replaced with said polypeptide fragment, induces apoptosis *in vitro* when over-expressed in human

breast carcinoma cells [wherein said nucleic acid encodes a polypeptide fragment which is capable of functioning as a functional domain within a mature DR5 polypeptide to induce apoptosis].

615. (Once Amended) A method of producing a vector that comprises inserting the polynucleotide of claim [606] 608 into a vector.

622. (Once Amended) A method of producing [a] the polypeptide fragment encoded by the polynucleotide of claim 608 comprising culturing [the] a host cell [of claim 618] comprising said polynucleotide under conditions such that said polypeptide fragment is expressed, and recovering said polypeptide fragment, wherein said polypeptide fragment binds an antibody with specificity for a polypeptide consisting of amino acids 1 to 360 of SEQ ID NO:2.